## REMARKS

Claims 1-16, 21-29, 31-34, and 37 are pending in the application. No amendments have been made by the present response and no new matter has been added.

35 U.S.C. §103(a) (Obviousness)

At pages 3-5 of the Office Action, claims 1-4, 6-16, 29, 32-34, and 37 were rejected as allegedly unpatentable over Papahadjopoulos et al, U.S. Patent No. 6,803,053 ("Papahadjopoulos") taken with Rolland et al., U.S. Patent No. 6,040,295 ("Rolland") and further in view of Lunsford et al., U.S. Published Application No. 2002/0182258 ("Lunsford"). In addition, claims 1-4, 6, 7, 9-16, 26, 29, 32-34, and 37 were rejected as allegedly unpatentable over Papahadjopoulos taken with Rolland and further in view of Mathiowitz et al., U.S. Patent No. 6,677,313 ("Mathiowitz").

Applicants respectfully traverse the rejection in view of the following comments.

Independent claim 1 is directed to a microparticle that is less than about 100 microns in diameter and contains: (i) a polymeric matrix; (ii) a lipid having a pKa of less than about 2.5; and (iii) a nucleic acid molecule, wherein the microparticle is not encapsulated in a liposome and the microparticle does not comprise a cell. Independent claim 21 is directed to a microparticle that is less than about 100 microns in diameter and contains: (i) a polymeric matrix; (ii) a lipid having a pKa of less than about 2.5; and (iii) a nucleic acid molecule.

The Office Action dated October 6, 2005 acknowledged that "Papahadjopoulos *et al.* does not teach that the complexes can be further entrapped within polymeric microparticles with a diameter of less than about 100 microns that are used in the prior art to prolong the controlled release and bioavailability of a nucleic acid plasmid complex." The rejection appears to be based upon the assertion that "it would have been obvious for one of ordinary skill in the art to employ known polymeric microparticles such as those disclosed in Lunsford to entrap and enhance the stability of the lipid:nucleic acid:PEG-DSPE complexes of Papahadjopoulos *et al.*" The Office Action dated October 6, 2005 stated that one of ordinary skill in the art would have been motivated to do this because "Rolland teaches that not only polymeric microparticles can be used

to enhance and prolong the bioavailability of naked plasmid vectors encoding a product of interest, the microparticles can also be used to do the same with nucleic acid plasmid vectors presented in various formulations." The Office Action also stated that one "would have been motivated to do so in order to enhance the controlled release of the lipid:nucleic acid complexes of Papahadjopoulos *et al.* and protect the plasmid vectors from degradation during its circulation *in vivo*." The Office Action used very similar language to that reproduced above in the obviousness rejection citing the combination of Papahadjopoulos, Rolland, and Mathiowitz.

Applicants respectfully contest the suggestion that the skilled person would have had any reason to entrap a lipid:nucleic acid:PEG-DSPE complex disclosed in Papahadjopoulos within a microparticle described in Lunsford or Mathiowitz.

Papahadjopoulos describes lipid:nucleic acid complexes containing, among other components: (a) a cationic lipid; (b) a nucleic acid; and (c) a hydrophilic polymer. Papahadjopoulos describes polyethylene glycol distearoyl phosphatidylethanolamine (PEG-DSPE) as an exemplary hydrophilic polymer that can be used in the complexes disclosed therein. According to Papahadjopoulos, a hydrophilic polymer is incorporated into the lipid:nucleic acid complex so as to prevent complexes from aggregating during storage and, as a result, increase the shelf life of the complexes. The hydrophilic polymer's role in preventing aggregation of the lipid:nucleic acid complexes is emphasized throughout Papahadjopoulos as an important advantage of the invention (see Papahadjopoulos at, e.g., column 13, lines 26-49, column 18, lines 32-40, and column 29, lines 30-36).

Lunsford describes microparticles containing a polymeric matrix, a nucleic acid, and a lipid. Similarly, Mathiowitz describes microparticles containing a polymeric matrix and a nucleic acid. As noted above, the reason for including a hydrophilic polymer (e.g., PEG-DSPE) in the lipid:nucleic acid complexes of Papahadjopoulos was to prevent aggregation of the complexes. The need to prevent lipid:nucleic acid complex aggregation would clearly be absent if a lipid:nucleic acid complex of Papahadjopoulos were to be entrapped in a microparticle of Lunsford or Mathiowitz (i.e., the lipid:nucleic acid complexes would be entrapped in microparticles and thus would be unable to aggregate). Because of the particularized anti-

aggregation function mediated by Papahadjopoulos's hydrophilic polymer, and the irrelevance of that function in the microparticles of Lunsford and Mathiowitz, the skilled person would have had no reason to entrap a hydrophilic polymer-containing lipid:nucleic acid complex of Papahadjopoulos in a microparticle of Lunsford or Mathiowitz. Furthermore, even if one were to attempt to entrap selected components (e.g., a cationic lipid and a nucleic acid) of a Papahadjopoulos composition in a microparticle of Lunsford or Mathiowitz, the skilled person would have had no reason to also include a hydrophilic polymer (e.g., PEG-DSPE) in such a composition. The need to prevent aggregation of lipid:nucleic acid complexes that was the rationale for Papahadjopoulos's inclusion of a hydrophilic polymer in its complexes would be absent in Lunsford's and Mathiowitz's microparticle formulations. As a result, the skilled person would have had no reason to create the combined composition suggested in the Office Action.

In view of the foregoing comments, applicants respectfully submit that the cited references do not render obvious any of claims 1-4, 6-16, 26, 29, 32-34, and 37.

At pages 5-7 of the Office Action, claims 21-24, 26-28, and 31 were rejected as allegedly unpatentable over Lunsford in view of Papahadjopoulos. According to the Office Action, "it would have been *prima facie* obvious for one of ordinary skill in the art to include PEG-DSPE disclosed by Papahadjopoulos *et al.* in the microparticle of Lunsford et al., with a reasonable expectation of success, to produce the microparticle of the instantly claimed invention."

Applicants respectfully traverse the rejection in view of the following comments.

As noted above, independent claims 1 and 21 are each directed to a microparticle that is less than about 100 microns in diameter and contains a polymeric matrix, a lipid having a pKa of less than about 2.5, and a nucleic acid molecule.

Lunsford describes microparticles containing a polymeric matrix, a nucleic acid, and a lipid. Lunsford does not describe or suggest including in a microparticle a lipid (such as PEG-DSPE) having a pKa of less than about 2.5. As detailed above in response to the previous obviousness rejections, Papahadjopoulos describes the inclusion of PEG-DSPE in lipid:nucleic

acid complexes as a means to prevent aggregation of the complexes and thereby enhance their shelf life. This function of PEG-DSPE in the complexes of Papahadjopoulos would be irrelevant in the microparticles of Lunsford. As a result, the skilled person would have had no reason to include a lipid such as PEG-DSPE in a microparticle of Lunsford.

In view of the foregoing comments, applicants respectfully submit that the cited references do not render obvious any of claims 21-24, 26-28, and 31.

## CONCLUSION

Applicants respectfully request that all claims be allowed in view of the remarks contained herein.

Enclosed is a Petition for Extension of Time and a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 08191-018001.

Respectfully submitted,

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